July 1, 2003

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Director,
Office for Human Research Protections
The Tower Building, Suite 200
Rockville, MD 20852

Re: Subpart D Panel Review

Dear Dr. Schwetz:

The following is my independent opinion upon participation with the Office for Human Research Protections and the Department of Health and Human Services expert panel review on June 17, 2003 of research under 45 CFR 46.407 of the protocol entitled "HIV Replication and Thymopoiesis in Adolescents", Dr. Paul Krogstad, Principal Investigator.

Dr. Krogstad hypothesizes that adolescents who experienced prolonged and poorly controlled HIV infection throughout childhood causes premature immunological aging, perhaps by accelerating changes in the thymus that cannot fully be reversed by highly active antiretroviral therapy (HAART). The thymus is a gland that makes T cells that help to fight infections.

The review focused specifically on the sub study that includes participants from all three age-matched cohorts; perinatally infected adolescents, adolescents infected through adult behaviors, and uninfected adolescents between the ages of 13 and 21. Specifically, the participants will be required to stay 24 hours in the Clinical Research Center. During this time, one group will receive glucose containing the stable isotope deuterium administered by I.V. infusion. This is a non-radioactive solution that "labels" lymphocytes. At various times after the infusion ("labeling period") blood will be drawn to measure the absolute rates of lymphocyte production. Another group will be required to drink a labeled water solution over the 24-hour stay and drink the water solution two to three times per week for following four weeks.

Meets General Criteria of 45 CFR 46.111
It is my opinion that this protocol is timely and of high importance and has the potential to provide important information regarding a population that little is known about. The answer to physiological changes during puberty and post puberty is crucial to understanding how the immune system responds to fight diseases and treatments. This study proposes to look at how the thymus functions in adolescents and young adults who are infected with HIV, compared to those in the same age group who are not infected with HIV.

Selection of the participants is equitable. There will be three age-matched cohorts; perinatally infected adolescents, adolescents not infected with HIV, and adolescents recently infected with HIV via adult behaviors. Many of the participants, particularly those in the control groups, will be recruited at the Risk Reduction Program at Children's Hospital Los Angeles. This program has successfully recruited, accrued and retained infected adolescents and adolescents who are at

high risk of becoming infected in its participation on the Adolescent Medicine HIV/AIDS Research Network and Pediatric AIDS Clinical Trials Group studies.

Balance of Risk to Benefit and/or Knowledge Applying Sub Part D
I believe that the risks to the study participants are reasonable in relation to the importance of the knowledge that will be gained by conducting the protocol. However, the Informed Consents and Assents must be revised to provide a better explanation of the participation requirements, procedures and test results that the participant can expect to receive in order to protect the rights and welfare of the adolescents.

Level of Risk of the Procedures
I respectfully disagree with the determination of the University of California, Los Angeles Institutional Review Board and do not find that any of the procedures for the main study or sub study listed below are of greater than minimal risk as defined by *45 CFR 46.404 Research not involving greater than minimal risk.*

1. Blood Collections;
2. CT Scan;
3. 24-hour infusion of deuterium; and
4. 24-hour water deuterium solution, followed by drinking the water solution two or three times a week for the next four weeks.

Blood collections – participants who are HIV infected are allowed to get their blood drawn during regularly scheduled clinic appointments for their general HIV care. Those participants who are not HIV infected, but attend the Risk Reduction Program and have participated in previous studies, have routinely had their blood drawn and should not have trouble with this requirement.

CT Scan – Dr. Krogstad provided sufficient information to the panel regarding the amount of radiation that the participant will be exposed to with the CT Scan. In addition, although an MRI would remove the radiation exposure issue, other issues such as availability of the MRI and the length of time that an MRI takes, makes it more of an imposition to the participant. As a matter of practice, CT Scan technicians always ask female patients if they are pregnant, thus reducing the risk of prenatal radiation exposure.

Twenty-four hour infusion of deuterium – The Clinical Research Center should be equipped to provide a comfortable setting for a twenty-four hour stay for the participant. Dr. Krogstad agreed that the participant would be asked if he or she is glucose intolerant. Topical creams can also be applied to help with the discomfort of inserting the I.V. needle into the vein.

Twenty-four hour water deuterium solution with follow up over four weeks - The Clinical Research Center should be equipped to provide a comfortable setting for a twenty-four hour stay for the participant. Dr. Krogstad agreed that the participant would be asked if he or she is glucose intolerant. Staff will also be available to observe possible adverse side effects from drinking more water than normal.

Requirements for Parental Permission and Child Assent
In general I found the language of the Informed Consents and Assents to be at the appropriate reading level and non-coercive. However, better descriptions of the procedures and associated risks would allow for a better informed consent or assent. Also, safe guards for protecting the participant's identity should be clearly stated. I appreciated that in the Informed Assent that the adolescent was told that they could decide not to participate even if their parent had consented.

Other
Specific Characteristic Among Cohorts - Although some of the participants are not infected with HIV, they are being recruited from a group identified to be at high risk of becoming infected due to their behaviors. These risk behaviors are the same as those in the group who became HIV infected as adolescents or young adults. Sadly, almost a quarter of new HIV infections are in adolescents and young adults under 25 years old. Thus, the information gained from this protocol will benefit more than perinatally infected adolescents and it is important to get information from each group at the same ages.

Sample Remaining at the End of the Study and Information About Your Sample – The Informed Consent and Informed Assent do not clearly distinguish between samples remaining at the end of the study and receiving information about the results from blood samples taken for the purposes of the study. Language needs to be changed to clearly state that if any blood samples remain at the conclusion of the study that the participant agrees that they can be shared with other researchers not part of the study. With regard to receiving information specific to the study that is learned from the samples, the section needs to clarify that not all information is sharable, and clarify what they can tell them during the course of the study. This section also needs to clarify whether or not they are offering to give general information about the knowledge gained from the study.

Adequate Privacy Protections – In addition to what I have stated above, protections with regard to disclosure must be protected, and assurances that if the adolescent chooses to withdraw, they do not have to express their reason in front of a parent of guardian.

Conclusion
As the parent of a perinatally HIV infected adolescent diagnosed in 1987, I know what it is to be without any treatment options for my child. I watched my child's health slowly deteriorate and felt helpless and frustrated about how slow the process is for developing research for new drug therapies. I waited anxiously for the day that the protease inhibitors were approved and was delighted that my child responded so well to them and is still doing well today.

I wanted to be better informed about the research that was in process as well as to be able to have input in the research that would be and was being developed. I decided to become active in the research process as a community member in my local Pediatric Community Advisory Board and on a national level on the Pediatric Community Constituency Group of the Pediatric AIDS Clinical Trials Group.

Based on my personal experiences of participating on clinical trials and consenting for my child to participate on clinical trials, I believe in the importance and value of good, sound clinical

research. It has been my goal that my child will understand this as well and share the responsibility of participating in research protocols. I believe that involving the adolescent in the assent process is an excellent educational tool. Just as important as being honest and straightforward with the information, is respect for their privacy and dignity.

I appreciate the opportunity to participate in the expert panel review of this very important and interesting research protocol.

Sincerely,

Eva Powell
Parent